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Research Paper

Adverse financial and clinical burden of the use of prophylactic antibiotics in neurosurgical patients☆

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ABSTRACT

Background: Current guidance does not support the administration of prophylactic antibiotics in non-infected post-operative surgical cases including neurosurgery.

Materials and methods: This paper is a qualitative assessment, highlighting the economic cost of excessive antimicrobial prescription and the healthcare costs of the extra days of admission in hospital.

Results: One hundred and one neurosurgical cases were analysed in a single institution over a one-year period. The additional course of post-operative antibiotics has a cost of £56.72 and receiving prolonged post-operative antibiotics added on average £1121.10 to their admission bill. Up to 13.4 patients may have experienced an adverse drug event.

Conclusion: This paper reinforces the adherence to guidelines can aid in the reduction of adverse drug events, improve patient outcomes, and reduce costs associated with unnecessary drug prescriptions and administration.

Introduction

There is well founded guidance that the administration of pre- or intra-operative antibiotics, in certain procedures, is effective in the prevention of Surgical Site Infections (SSI) [1]. Current guidance does not however support the administration of prophylactic antibiotics in non-infected post-operative surgical cases including neurosurgery [2–4]. The administered antibiotics pre- or intra-operatively are determined by the hospitals local antibiotic formulary [1].

The National Health Service (NHS) has been pushing guidance out including through public awareness campaigns that the using and the overuse of antibiotics increases the risk of adverse side effects, for example, *Clostridium difficile* infection, in addition to the spectre of increased risk of antibiotic resistance in addition to allergy reactions that could also be life threatening [1]. These adverse drug events from prolonged antibiotic courses may inadvertently increase the length of stay, have adverse patient outcomes and drive healthcare provider costs [5,6]. Adhering to evidence-based guidance and its compliance provides a strong incentive to mitigate against the costs, both to the patient and healthcare provision.

The overuse of antibiotics and resistance is not only a United Kingdom (UK) public health issue, but also identified as one of the 10 health and development threats declared by the World Health Organization (WHO) [7,8]. The economic strain of antimicrobial resistance especially developing nation with fragile healthcare systems will undoubtedly be devasting. In the wake of SARS-COVID-19, most healthcare systems are in state of distress. Antimicrobial resistance and the lack of effective agents will universally put at risk the success of modern medicine from major surgery to cancer therapy [8].

Current National Institute of Clinical Excellence (NICE) guidelines state surgical antimicrobial prophylaxis should not be used routinely for uncomplicated, clean, non-prosthetic surgery. NICE recommends, if needed, a consideration of a single-dose intravenous on starting anaesthesia [1]. NICE does recommend giving one dose of prophylactic antibiotics for clean surgeries with prosthesis or implant, clean-contaminated procedures (such as transsphenoidal), contaminated procedures and for dirty or infected wounds [1]. The UK High Impact Intervention guidelines recommend giving Surgical Antimicrobial Prophylaxis (SAP) within 60 min prior to incision and only repeating if excessive blood loss, prolonged operation or prosthetic surgery [3]. WHO similarly

Abbreviations: SARS-COVID-19, Severe acute respiratory syndrome coronavirus disease 2019.

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Table 1
Demographics details of the cohort.

$N = 101$	Cranial surgery	Spine surgery without instrumentation	Spine surgery with instrumentation
Elective	27	16	18
Emergency	28	7	5
Total	55	23	23

recommend SAP should be administered within 120 min prior to surgical incision while considering the half-life of the antibiotic [2]. It further recommends against post-operative antibiotics, for the purpose of preventing SSI, in all types of surgical procedures [2].

The paper is a qualitative assessment, highlighting the economic cost of excessive antimicrobial prescription and the direct effect on reducing the outward healthcare costs of (i) the extra days of admission in hospital and (ii) the possibility of adverse drug events [2–4,9]. A secondary outcome, while not in the scope of the paper, is to hopefully let clinicians take stock of sequalae of prescribing prophylactic antibiotic use post-operatively and thereby improving compliance with local and international guidelines. In turn it should be these small tangible aims the help battle the challenges of antibiotic resistance.

Methods

One hundred and one (101) neurosurgical operative cases were identified during the time frame, between May 2020 to August 2020 at a single institution. Cases of pre-operative infection or collection requiring antibiotic treatment post-operatively have been excluded. Information has been collected from both physical notes as well as theatre notes on the internal hospital system on all the eligible surgical cases. Data collected included the type of procedure, the American Society of Anaesthesiologists (ASA) grade, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) category and the duration of post-operative antibiotics [10,11]. The co-morbidities of patients is categorised by the American Society of Anaesthesiologists (ASA) grading system [10].

The data is categorised as defined by the NICE guidelines dividing the cohort into two, (i) no administration of antibiotics and (ii) a second group that have at least one dose antibiotics administered or more [1]. A further categorisation of the data is represented in results by the length of the antibiotic course - no post-operative antibiotics, 1 dose, 2 doses, 3 doses, a 2-to-5 day course or a 5 day or longer course. Data is also categorised based on the type of procedure to include cranial procedures, spinal procedures and spinal procedures with implants or devices. The WHO categories for clean, clean-contaminated, clean with implant or device, contaminated and dirty is used in addition. These categories were chosen as they generally form the basis of antibiotic guidelines. In accordance with the exclusion criteria, any contaminated or dirty wound operations were not included, as these cases would require post-operative antibiotics. The cases are further categorised in accordance with whether it was an elective or emergency operation.

The specific antibiotic regimes are recorded and there is a common dosing of six antibiotics for the 101 neurosurgical operatives including Gentamicin, Metronidazole, Teicoplanin, Cefuroxime, Flucloxacillin and Vancomycin. The adverse antibiotic costs are derived from the British National Formulary (BNF) and local trust procurement [12]. The excess days of admission financial costs is taken from the NHS National Tariff Payment System 2016/17 (£351 per day) [13].

The statistical analysis is performed using GraphPad by Dotmatics online statistical calculator (https://www.graphpad.com/quickcalcs/). Two statistical tests are used to compare the two cohorts, (i) no administration of antibiotics and (ii) one or more doses are administered - an unpaired two-tailed t-test to indicate whether age is significant and a two-tailed Fisher's exact test on the significance of ASA grade (i.e., co-morbidities).

The data was compared to local and international guidelines for prophylactic antibiotic use to prevent SSIs. The research is carried out in accordance with local ethical protocols and approval by the local ethical committee (reference number 755).

Results

One hundred and one neurosurgical cases were reviewed over a one-year period (Table 1). The mean age is 57.3 years, median 57 year (range 32 to 86) with 47 females and 54 males. If the NICE guidelines is adhered, it divides the cohort into two, (i) no administration of antibiotics and (ii) a second group that have at least one dose antibiotics administered or more [1]. 35 patients did not receive any post-operative antibiotics, 57.2 years, median 56 year (range 32 to 84) with 15 females and 20 males. 66 patients did receive at least on dose of post-operative antibiotics, 57.3 years, median 56.3 year (range 38 to 64) with 32 females and 34 males. There is no difference in the age distribution between the two groups (unpaired two-tailed t-test, $p = 0.9494$).

Of the grade ASA grade 1 cohort ($n = 4$) i.e., with no medical comorbidities, three patients were not administered post-operative antibiotics and only one patient administered one or more doses of antibiotics. Of the patients ASA grade 2 or more, 32 had no post-operative antibiotics prescribed and 65 patients one dose or more. Medical comorbidities i.e., ASA grade did not impact on whether post-operative antibiotics was prescribed (two-tailed Fisher's exact test, $p = 0.1186$).

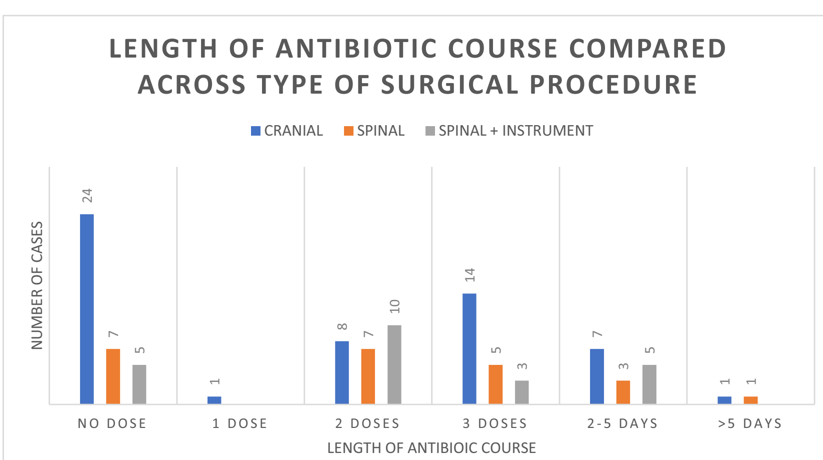

Fig. 1. Length of antibiotic course compared across type of surgical procedure.

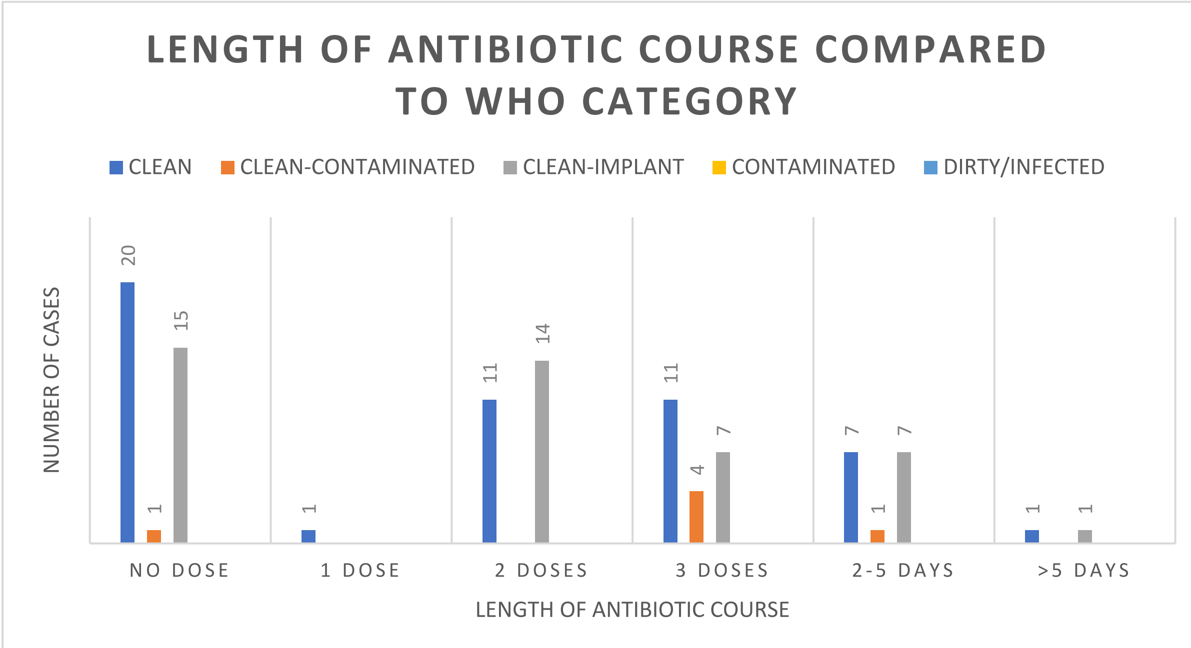

Fig. 2. Length of antibiotic course compared to WHO categories.

A demographic breakdown of the 101 cases (Table 1), the majority of the cases are cranial ($n = 55$) and the rest spine ($n = 46$).

A considerable variability of the length of course of antibiotics post-operatively across all procedures within the same category of procedure (Fig. 1). A third ($n = 36$) received no antibiotics post-operative antibiotics although a majority have been administered at least one dose. 47 patients received 2 or 3 doses of antibiotics.

The length of antibiotic courses with the WHO categories excluding contaminated procedures or dirty wounds (Fig. 2).

The length of the antibiotic course with the urgency of the operation was further compared, with the category of elective cases (NCEPOD 1–2) and emergency cases (NCEPOD 3–4) (Fig. 3).

The neurosurgical case load against the length of antibiotics course represented according to NCEPOD category (Fig. 4) and ASA grading (Fig. 5). A majority of the elective cases ($n = 28$) had one or more doses of antibiotics administered (Fig. 4).

The last graph looks at cases that received 3 or more doses were deemed as a prolonged course of antibiotics (Fig. 6). A trend of elective cases to be given longer antibiotics courses.

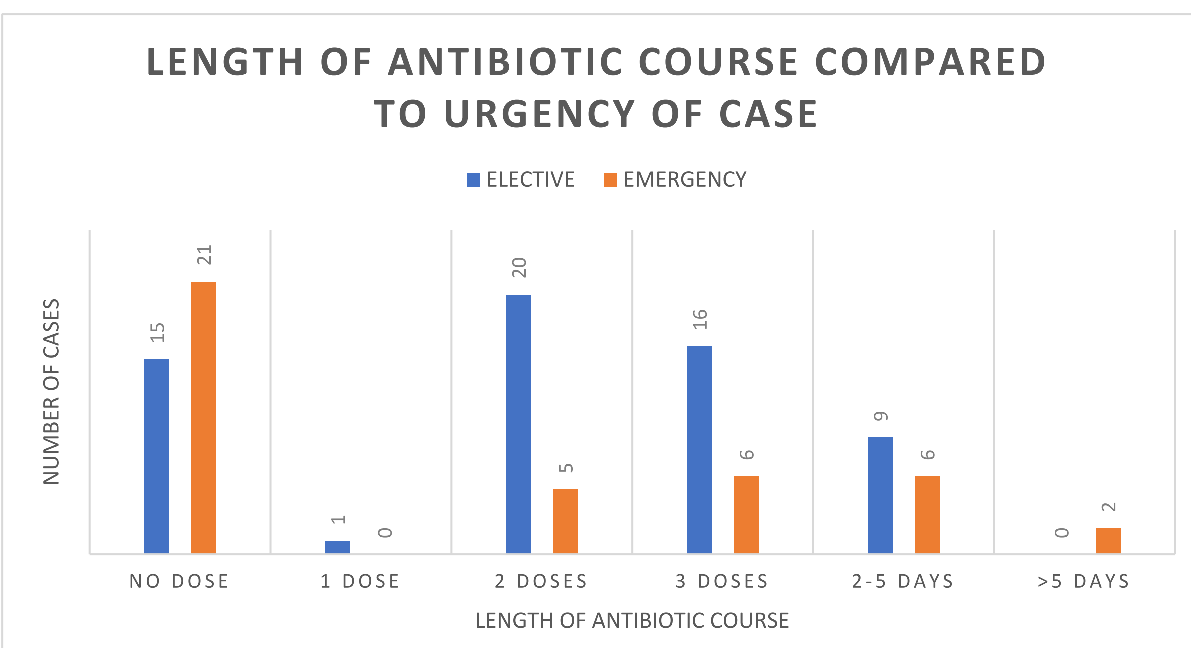

Fig. 3. Length of antibiotic course compared to urgency of case.

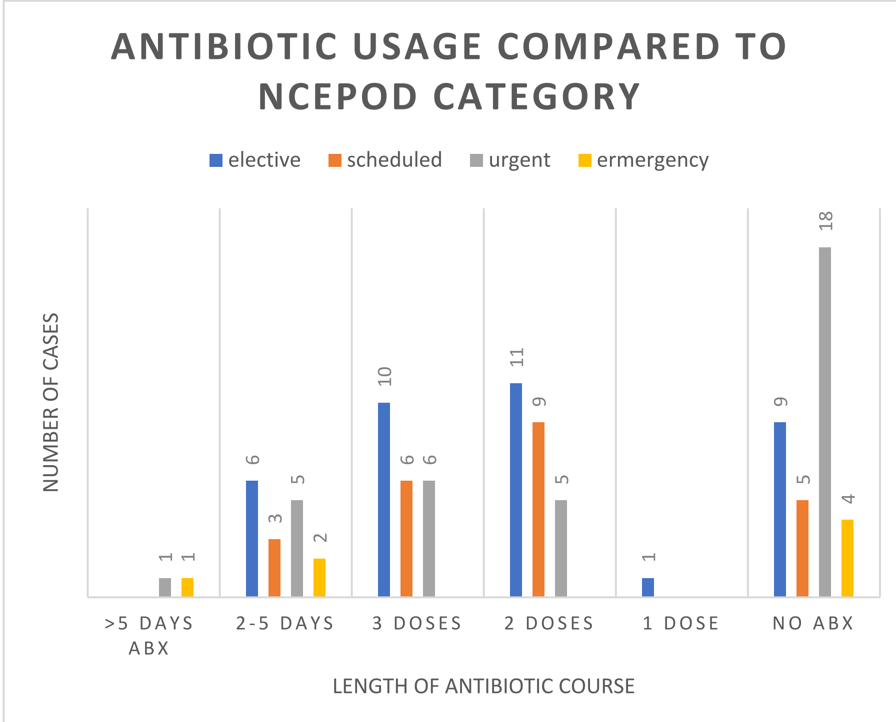

Fig. 4. Length of antibiotic course compared to NCEPOD categories.

Cost of antibiotics and post-operative hospital admission

The additional course of post-operative antibiotics added a further £56.72 to the inpatient cost excluding direct/indirect healthcare related costs. On factoring in the additional bed days, which will cost upwards of £351, the cohort that received prolonged post-operative antibiotics added a further on average £1121.10 to their admission bill [13].

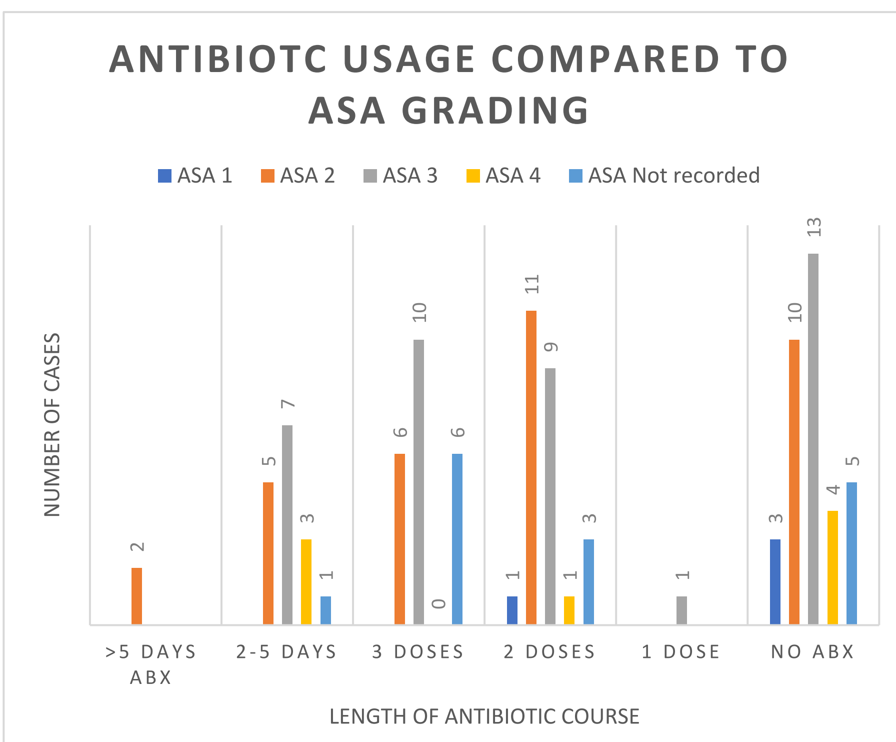

Fig. 5. Length of antibiotic course compared to ASA grading.

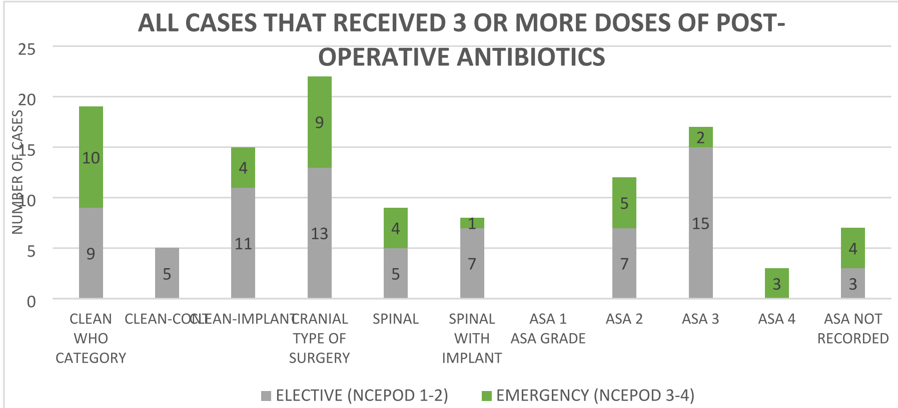

Fig. 6. Cases which received prolonged course of antibiotics compared across each category.

Discussion

Over the last couple of decades surgical sciences have moved progressive with advancing methods to reduce the complications associated with surgical site infections (SSI) [1]. Complications in neurosurgery can be catastrophic with significant associated morbidity and mortality [14–16].

At this single institution this is only 35 % compliance rate with the current guidelines. In 64 % of cases, patients received prolonged post-operative antibiotics, with 17 % of cases receiving over 48 h of antibiotics. High levels of variability across all procedures were observed, with no predictability of when prolonged courses may be prescribed. Spinal surgery (Fig. 1) was broken down into two subgroups, with and without instrumentation, as the surgeons would often prescribe a course of post-operative antibiotics ($n = 18$, 72 %) than not ($n = 5$, 28 %).

A qualitative breakdown of the neurosurgical interventions reveals that five shunts were performed in the period under investigation, three of which received antibiotics and two were not. A single case that received a course of antibiotics underwent a revision of Ventriculo-Peritoneal (VP) shunt, although notoriously insertion VP shunts are known for high complications (up to a third within 30-days) associated with blockage and/or infection [15–18]. It would perhaps explain the reticence by some professionals not to prescribe antibiotics. Another source of high complications can be from the insertion of External Ventricular Drain (EVD) catheters, as these catheters into the ventricular system are exposed to the environment [17,18]. Five EVD catheters were inserted, three received prolonged doses of antibiotics including an EVD inserted secondary to an Endoscopic Third Ventriculostomy (ETV) and another patient that underwent a post-fossa decompression, and two did not receive any further post-operative dose. Another class of neurosurgical cranial intervention associated with high rates of infection is the insertion of artificial prosthesis for cranial skull defect, cranioplasty and often rates of infection can range as high as 33 % not forgoing other complications associated with it [19]. Two of the 101 neurosurgical interventions underwent this procedure, and both received antibiotics.

The trend from the data analysis shows a trend for elective cases to be given longer antibiotics courses although no deducible clinical pattern for these cases of prolonged antibiotic usage (Fig. 6). There is no significant difference in the age between the cohort that were not and were given at least one dose of antibiotics. Patients with 1 or more comorbidity (ASA grade 2 or greater) are no more likely to receive antibiotics than patients with an ASA grade 1. The two patients that received 7 days of post-operative antibiotics had an ASA grade 2, one undergoing an urgent lumbar spine laminectomy and another an emergency decompressive craniectomy for an acute subdural haematoma. Six patients underwent a transsphenoidal endoscopic pituitary surgery that is considered clean contaminated. One patient, ASA grade 3, received no post-operative antibiotics and five at least one dose of antibiotics.

As alluded to in the evidence and local, national as well as international guidance, the administration of pre- or intra-operative antibiotics, in certain procedures, is effective in the prevention of SSI [1]. The same guidance does not support the administration of prophylactic antibiotics in non-infected post-operative surgical cases including neurosurgery [2–4]. The hesitance to not prescribe could be attributed to numerous clinician concerns including the potential of adverse outcomes whether it is severe morbidly or death. Post-operative antibiotics are more likely to be given for more than 5 days in emergency procedures category, Figs. 3 and 4, as for clinicians there is a perception of risk if the surgery is urgent or an emergency. It should also be borne in mind the increasing hostility of the professional regulatory environment and that surgeons may have to face accusations of negligence if they do not conform to a perceived normative practice [20,21].

Another consideration while not within the scope of this paper is clinicians' practices outside the NHS i.e., private practice and the ramifications to complications including high medical indemnity costs and reputational damage.

Cost of antibiotics. The NHS healthcare budget is not finite, in the year 2020/2021 it was £159 billion and tangible costs account for a significant proportion including pharmaceutical and hospital bed days [22]. The additional course of post-operative antibiotics adds a further £56.72 to the inpatient bill and this excludes direct/indirect care related costs i.e., nursing time. On factoring in the additional bed days that can cost upwards of £351, for those that had received prolonged post-operative antibiotics, it adds on average £1121.10 to the admission bill, only inclusive of the cases receiving 2 or more days of antibiotics [13]. The total cost for the year accumulates to £31,941 for the minimal days required for each dosing regimen although this can be up to £75,114, if considered for all the 65 cases that received 1 or more doses of antibiotics. To complicate this picture, neurosurgical cases are often complex, and patients may often have protracted post-operative admissions. An indirect consequence of increase bed days is the associated issue of increased bed occupancy that has the effect of reducing the turnover of patients i.e., referred to as bed blocking, over the course of a year will impact on the number of surgeries performed.

Risk of adverse drug events. The risk of an adverse drug events from increase antibiotics prescribing should be another area for consideration notwithstanding complications, sequalae of prolonging admissions and increased cost to the trust. The data was not recorded but this serves as an exercise to estimate the consequences, juxtaposing to our data against known data on adverse drug events with antibiotic administration [6]. If 65 patients received prolonged course of antibiotics, there would have been 13.4 patients that experienced an adverse drug event, 12 cases of *Clostridium difficile* infection and 18.8 cases of multidrug-resistant organism infections within 90 days of antibiotics. These risks are not usually conveyed to patients during the consent process [23,24].

Limitations. For those cases that received prolonged courses of antibiotics, possible clinical reason for deviation from international standards were not recorded within audit data. The data encompassed a record of ASA grading to assess the potential risk level of each patient. The data did not include the pre or intra operative antibiotics, it was not possible to assess if the prophylactic antibiotic guidelines of giving the dose prior to first incision were being met. The notes were not accessible as the trust has migrated to a digital platform. The type of antibiotic prescribed were not recorded, not allowing assessment whether adherence to local guidelines for specific antibiotics used was occurring. Variables such as the timing of first post-operative antibiotic dose following surgery or adverse events, length of stays, whether discharge was delayed due to antibiotics were also not recorded. These variables and correlation to such guidelines was the scope of the current audit aims and objectives.

Conclusions. Prophylactic antibiotics are not always needed for clean, un-complicated procedures without implants. Adherence of guidelines can aid in the reduction of adverse drug events, improve patient outcomes, and reduce costs to the Department and Trust whether it is a hospital in the UK or any other nation. Patients should receive one dose of antibiotics preferably pre-operatively (within 120 min of surgical incision), with a second dose of antibiotics intra-operatively if there is excess blood loss, devices/prosthesis are implanted or if the surgery is over six hours. The unnecessary additional course of post-operative antibiotics adds a further £56.72 per patient and taking into account a prolonged stay to administer these antibiotics, it adds on average a further £1121.10 to the admission bill. For developing economies, the additional costs can be detrimental to healthcare equity.

CRediT authorship contribution statement

Naairah Khan – formulation of the paper; Zairah Shamshad – data collection & analysis; Holly Batchelor-Parry – data collection & analysis; Iqra Marriyam – data collection & analysis; Sayed Samed Talibi – review of the data analysis & draft paper; Rahim A Hussain – conceptualisation & senior author.

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Ethics approval

The research was carried out in accordance with local ethical protocols and approval by the local ethical committee (local reference number 755).

Declaration of competing interest

There is no conflict of interest of any of the authors.

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